Tandem Rh(I)-Catalyzed [(5+2)+1] Cycloaddition/Aldol Reaction for the Construction of Linear Triquinane Skeleton: Total Syntheses of (+)-Hirsutene and (+)-1-Desoxyhypnophilin

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Linear Triquinanes: Target Natural Products

- Polyquinane natural products were first isolated in 1966.
- Since then over 80 linear triquinane natural products have been isolated from plants, microbes and marine organisms.
- Biological activities of select linear triquinanes include antibiotic and antitumor activity.

Background: Theoretically Suggested Mechanism for [Rh(CO)\(_2\)Cl\(_2\)] \(_2\) Catalyzed Intermolecular (5+2) Reactions between Vinylcyclopropanes and Alkynes

![Catalytic Cycle]

\[ \text{1/2 [Rh(CO)\(_2\)Cl\(_2\)]}_2 \rightarrow \text{R} \text{R} \text{R} \rightarrow \text{Rh(CO)Cl} \rightarrow \text{Rh} \text{Rh} \text{Rh} \rightarrow \text{Cyclohexane} \]

Could the Intermediate Along the Route to a [5+2] Cycloaddition be intercepted by CO to give a [5+2+1] Cycloadduct

\[ \text{CO insertion} \]

\[ \text{[5+2] product} \]

Yes… With a Surprising Result!

\[
\text{CO}_2\text{Me} + \text{CO}_2\text{Me} \xrightarrow{\text{CO (1 atm), } [\text{Rh(CO)}_2\text{Cl}]_2} \xrightarrow{\text{DCE, } 60 \, ^{\circ}\text{C}, \text{H}_3\text{O}^+} \]

13% 18% 32%

Transannular Aldol condensation gives the corresponding diquinane products

- Good yields of diquinanes with carbonyl activated alkynes
- Highly regio- and diastereoselective

Background: Rh(I)-Catalyzed Two Component [5+2+1] Cycloaddition of Ene-vinylcyclopropanes and CO

Computational considerations for the [Rh(CO)₂Cl]₂ catalyzed cycloaddition reaction

Effect of VCP olefin geometry on the cis/trans stereochemistry of the bicyclic products

Substrate Scope

Combination of Methodologies: Construction of the Linear Triquinane Skeleton

• Key Transformation

\[
\text{ene-VCP} \xrightarrow{\text{Rh(I)-catalyzed} \quad [(5+2)+1] \quad \text{cycloaddition}} \quad \text{linear triquinane}
\]

• Initial Attempts

\[
\text{methoxyethoxy-ene-VCP} \xrightarrow{i) \text{ CO (1 atm), 5 mol % } [\text{Rh(CO)}_2\text{Cl}]_2, \quad \text{dioxane, 60 °C, 32 h}} \quad \text{Complex mixture} \\
\quad \quad \xrightarrow{\text{ii) HCl-H}_2\text{O}} \\
\text{methoxyethoxy-ene-VCP} \xrightarrow{i) \text{ CO (0.2 atm), 5 mol % } [\text{Rh(CO)}_2\text{Cl}]_2, \quad \text{dioxane, 80 °C, 24 h}} \quad \text{16%}
\]
Optimization: Changes at the O-substituent

• Ethoxy- and siloxy-ene-VCP

i) CO (0.2 atm), 5 mol % \([\text{Rh(CO)}_2\text{Cl}]_2\) dioxane, 80 °C, 24 h

ii) HCl-H2O

Complex mixture

Ethoxy-ene-VCP

Siloxy-ene-VCP

19%
Model Reaction Study on the Tandem Two-Component [(5+2)+1]/Aldol Reactions

- Different tether groups on the siloxy-ene-VCPs have a minor effect on the reaction

- Methyl substituted (Z)-siloxy-ene-VCPs produce the correct cis-anti-cis configuration of the linear triquinane core diastereoselectively

- Methyl substituted (E)-siloxy-ene-VCPs produce the trans fused 5-8 bicyclic compounds and do not undergo the tandem aldol reaction
Rational for the Stereochemistry of the [(5+2)+1] Cycloaddition

a. Stereochemical process for [(5+2)+1] cycloaddition:

- **Mechanism:** VCP cleavage, alkene insertion, CO insertion, reductive elimination

![Diagram of the cycloaddition process]

- **TS1-cis** (less ring strain): cis cycloadduct
- **TS1-trans** (more ring strain): trans cycloadduct
- **TS2-cis** (steric repulsion): cis cycloadduct
- **TS2-trans**: trans cycloadduct

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Rational for the Stereochemistry of the Aldol Condensation

• The stereochemical outcome of the tandem two-component [(5+2)+1]/aldol reaction diastereoselectively sets the tricyclic core of hirsutene and 1-desoxyhypnophilin
Retrosynthetic Analysis for the Natural Products: hirsutene and 1-desoxyhypnophilin

Both natural products can be synthesized by elaboration of the common linear triquinane intermediate resulting from the tandem Rh(I)-catalyzed [((5+2)+1)/aldol reaction methodology.
Synthesis of Key linear triquinane intermediate and (+)-Hirsutene

Concise 8 step synthesis of (+)-hirsutene with an overall yield of 11%
Synthesis of (+)-1-Desoxyhypnophilin

(+)-1-desoxyhypnophinin synthesized in 9 steps with 13% overall yield
Conclusions

• The authors have developed an efficient tandem two-component rhodium(I) catalyzed [(5+2)+1] cycloaddition/aldol condensation reaction.

• This methodology was showcased by diastereoselectively establishing, in a single step, the correct placement of all stereocenters, including the two quarternary centers, contained in the core structure of the linear triquinanes: hirsutene and 1-desoxyhypnophilin.

• This paper represents the first application of the Rh(I)-catalyzed [(5+2)+1] methodology in natural product synthesis.

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\text{(+)-1-desoxyhypnophilin} \quad \text{(+)-hirsutene}
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